



National
Library
of Medicine

Entrez	PubMed	Nucleotide	Protein	Genome	Structure	PMC	Journals	Books
Search	PubMed	<input type="text"/> for <input type="button" value="Go"/> <input type="button" value="Clear"/> <input checked="" type="checkbox"/> Limits <input type="button" value="Preview/Index"/> <input type="button" value="History"/> <input type="button" value="Clipboard"/> <input type="button" value="Details"/>						
<input type="button" value="Display"/> <input type="button" value="Abstract"/> <input type="button" value="Show: 20"/> <input type="button" value="Sort"/> <input type="button" value="Send to"/> <input type="button" value="Text"/>								

Entrez
PubMed

1: Med J Aust. 2002 Sep 16;177(6):316-8.

Related Articles, Links

free text

Adult human neural stem cells for cell-replacement therapies in the central nervous system.

Galvin KA, Jones DG.

PubMed
Services

Department of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand.

Human neural stem cells (HNSCs) can be isolated from both the developing and adult central nervous system (CNS). HNSCs can be successfully grown in culture, are self-renewable, and can generate mature neuronal and glial progeny. Embryonic HNSCs can be induced to differentiate into specific neuronal phenotypes. HNSCs successfully integrate into the host environment after transplantation into the developing or adult CNS. HNSCs transplanted into animal models of Parkinson's disease and spinal cord injury have induced functional recovery. The risks associated with stem cell transplantation trials are difficult to assess, but have not become overtly apparent throughout preclinical investigations. Major hurdles remain to be overcome before human clinical trials can be embarked upon.

Related
Resources

Publication Types:

- Review
- Review, Tutorial

PMID: 12225280 [PubMed - indexed for MEDLINE]

Display	Abstract	<input type="button" value="Show: 20"/>	Sort	<input type="button" value="Send to"/> <input type="button" value="Text"/>
---------	----------	-----------------------------------------	------	----------------------------------------------------------------------------

[Write to the Help Desk](#)

[NCBI](#) | [NLM](#) | [NIH](#)

[Department of Health & Human Services](#)

[Freedom of Information Act](#) | [Disclaimer](#)



eMJA

[Home](#) | [Issues](#) | [Classifieds](#) | [More...](#) | [Topics](#) | [Search](#)

From Bench to Bedside

list for this issue
Adult human neural stem cells
for **cell-replacement therapies**
→More articles on Neurology
→Download a pdf version of this article
for →Search PubMed for related articles

in
the central nervous system

Kerry A Galvin and D Gareth Jones

MJA 2002 177 (6): 316-318

Abstract

- Introduction
- Isolating human neural stem cells
- Culturing human neural stem cells
- Controlling the phenotype
- Transplanting human neural stem cells into the central nervous system
- Transplantation into the developing CNS
- Transplantation into the adult CNS
- Risks to patients
- Clinical studies
- The way ahead
- Competing interests
- References
- Author details

Abstract

■ Human neural stem cells (HNSCs) can be isolated from both the developing and adult central nervous system (CNS).

- HNSCs can be successfully grown in culture, are self-renewable, and can generate mature neuronal and glial progeny.
- Embryonic HNSCs can be induced to differentiate into specific neuronal phenotypes.
- HNSCs successfully integrate into the host environment after transplantation into the developing or adult CNS.
- HNSCs transplanted into animal models of Parkinson's disease and spinal cord injury have induced functional recovery.
- The risks associated with stem cell transplantation trials are difficult to assess, but have not become overtly apparent throughout preclinical investigations.
- Major hurdles remain to be overcome before human clinical trials can be embarked upon.

A stem cell is an unspecialised cell which has the ability to renew itself indefinitely, and, under appropriate conditions, can give rise to a wide range of mature cell types in the human body. As any disorder involving loss of, or injury to, normal cells could be a candidate for stem cell replacement therapy, the potential of stem cells is profound. Stem cell therapy for the nervous system has generated particular interest because of the debilitating nature and widespread occurrence of neurodegenerative disorders.

The issue of stem cell research is politically and ethically charged, as so much emphasis has been placed on the use of stem cells derived from early human embryos. As a result, stem cell technology is imbued in an ethical conflict between destructive human embryo research on the one hand, and the magnitude of the potential benefits to patients, on the other. However, stem cells may be derived from a variety of sources, including early embryos, fetal tissue and some adult tissues (eg, bone marrow and blood).

Recently, a renewable resource of neural stem cells was discovered in the

adult human brain.¹ These cells may be a candidate for cell-replacement therapy for nervous system disorders. The ability to isolate these cells from the adult human brain raises the possibility of autologous (self-to-self) transplantation, which circumvents the logistical, safety and ethical issues surrounding transplantation of various other cell types (especially embryonic stem cells) into the human central nervous system (CNS).

There have been reports that clinical trials with adult human neural stem cells (HNSCs) have been, or are soon to be, initiated for Parkinson's disease.² In light of this, we assess the scientific potential of autologous transplantation of adult HNSCs for the treatment of CNS disorders such as Parkinson's disease and spinal cord injury.

Isolating human neural stem cells

The unequivocal localisation of neural stem cells in the human CNS remains elusive. However, HNSCs have been isolated from various regions of the embryonic,^{3,4} fetal^{5,6} and adult human brain, including the hippocampus, the ventricular/ependymal zone,⁹⁻¹² and, more recently, from the cortex and the amygdala.¹³ As far as is known, no one has attempted to isolate HNSCs from the adult spinal cord. However, some studies have reported isolating neural stem cells from the human fetal spinal cord.^{5,14}

HNSCs have been isolated from brain tissue obtained from patients undergoing surgical procedures involving removal of brain tissue for the treatment of epilepsy, tumours, or trauma. These studies demonstrate that the adult human brain contains a renewable source of neural stem cells which can be successfully isolated through various surgical techniques. This is encouraging in terms of autologous neural stem cell transplantation, where cells would be harvested directly from the brains of, for instance, patients with Parkinson's disease. The next key step is to show that the harvested cells are sustainable and expandable in long-term culture systems, and that they can be instructed to form specific neural cell types on demand.

Culturing human neural stem cells

HNSC culture is rapidly becoming more routine. Embryonic and fetal neural stem cells have shown remarkable functional stability and renewal

capacity for extended culture periods of up to two years.^{3,4} They spontaneously differentiated into the three fundamental neuronal lineages (neurones, astrocytes and oligodendrocytes) and were able to achieve full neuronal maturation.^{4,5}

It has been reported that cultures of stem cells derived from the embryonic human forebrain can be expanded up to ten millionfold *in vitro*.⁴ Such culture systems could provide an almost unlimited source of neural stem cells for cell-replacement strategies. If adult neural stem cells are to be used in clinical trials they must also be amenable to expansion into clinically significant quantities. Unfortunately, these cells seem to have a limited life-span in the culture dish,^{10,11} and it remains to be determined whether they are stable at later passages with regard to generating useful numbers of neurones. Adult human neural cells do, however, exhibit many of the promising characteristics of embryonic and fetal stem cells.

There are two major applications of HNSCs for the treatment of CNS disorders. Firstly, HNSCs could be transplanted as undifferentiated cells whose subsequent differentiation would be controlled by cues derived from the patient's brain. Alternatively, they could be predifferentiated in the culture dish into a desired neuronal type, which could then be transplanted back into the host brain. This latter option may be preferable because graft tissue could be "tailored" to specific applications (eg, pure cultures of dopamine neurones for Parkinson's disease). This option necessitates an ability to direct the differentiation of stem cells into desired neuronal phenotypes.

Controlling the phenotype

The problems associated with generating specific neuronal phenotypes from neural stem cells are not trivial. Currently, very little is known about the mechanisms that control differentiation in HNSC culture systems. What has become clear throughout the literature on rodents is that the major default phenotype for neural stem cells is gamma-aminobutyric acid (GABA)-producing neurones. This is unfortunate with regard to the use of these cells for the treatment of Parkinson's disease, where neurones that produce dopamine are obviously required.¹⁶ However, attempts to generate these neurones in cultures of rodent neural stem cells have met with some success.^{17,18} Similarly, a limited number of studies have shown that human embryonic and fetal neural stem cells can be induced to generate dopamine-producing neurones.^{3,20} Despite the positive nature of these reports, the numbers of neurones produced are very low.

As far as we know, there have been no published reports of the successful differentiation of adult HNSCs into dopaminergic neurones. The inability to consistently induce HNSCs to differentiate into specific neuronal phenotypes is currently the major stumbling block to using autologous neural stem cell transplantation as therapy for Parkinson's disease, and indeed other CNS disorders. On a more positive note, although the above data indicate that a dopaminergic phenotype is not a "default" choice of fate for HNSCs, given the right conditions some cells do have the capacity to form dopaminergic neurones *in vitro*. What we need now is to learn more about the mechanisms and signals involved in the control of stem cell differentiation.

Transplanting human neural stem cells into the central nervous system

It is of major interest to investigate the capacity of HNSCs to engraft into the brain in a functionally meaningful manner in well-characterised animal models of CNS dysfunction.

Transplantation into the developing CNS

Studies have shown that stem cells derived from the embryonic or fetal human brain can successfully graft into the developing rodent CNS.^{6,8} Once transplanted, these cells survived, migrated and integrated seamlessly into the host tissue, giving rise to cells from all three fundamental neuronal lineages. The grafted cells also replaced deficient neuronal populations in a model of neuronal degeneration in the mouse cerebellum.⁶

Transplantation into the adult CNS

Transplantation studies in the adult CNS are more challenging; as the environment is fully established, developmental cues are restricted, and space is more limited.¹⁶ Nevertheless, investigators have shown that stem cells isolated from the embryonic human brain survived and differentiated

into neurones and glia when grafted into various regions of the adult rat brain.⁴ Even more significantly, transplants of these cells were able to improve cognitive function in aged rats.²²

Currently, it is disorders like Parkinson's disease which are generating the most interest in terms of neural stem cell therapies. When stem cells derived from the developing human nervous system were transplanted into adult rats with a well-characterised model of Parkinson's disease (6-hydroxydopamine lesions), the cells survived for up to a year after transplantation, differentiated into neurones and astrocytes, and were able to decrease motor disturbances in some of the experimental animals.^{5,23} These observations, particularly that of functional recovery, hold great promise for humans.

To date, only one study has investigated the potential of *adult* HNSCs to restore anatomy and function in the injured adult CNS. In that study neural stem cells were transplanted into the demyelinated adult rat spinal cord.¹² These cells elicited extensive remyelination of the cord, and, when tested electrophysiologically, the axons conducted impulses at near-normal conduction velocities. Thus, not only was remyelination observed, but it was also functionally significant. This study is promising, but much more work is required. No stem cell transplantation studies have been carried out in primate models of neurodegenerative disorders. Primate models most closely mimic the human situation, and would allow potential risks and benefits to be more adequately assessed. This step should not be neglected in the rush to apply HNSC therapies to the clinic.

Risks to patients

A frequent concern is that the long-term propagation of stem cells *in vitro* could induce tumour formation. For instance, extensive culturing of rodent neural stem cells has been shown to lead to genetic changes that altered cell growth and differentiation.²⁴ However, tumour formation has not been observed in any culture systems of human CNS stem cells, or after transplantation into any animal models to date. Further experiments are needed to assess the tumorigenic potential of HNSCs.

Clinical studies

In the past, the vast majority of clinical transplantation trials for Parkinson's disease have attempted to replace dopaminergic neurones with transplants of different types of dopamine-producing cells, including adrenal medulla cells and human fetal cells.²⁵ Overall, the results have been moderately encouraging and no major risks have emerged. However, the paucity of long-term cell survival, risks of immunological rejection, logistical issues relating to the supply of tissue, and ethical concerns associated with the procurement of fetal tissue have precluded transplantation from becoming an acknowledged viable treatment option for Parkinson's disease. Despite this, transplantation studies have paved the way for the transplantation of stem cells in Parkinson's disease. The situation is far more complex for spinal cord injury. Restoring spinal cord function requires reconstruction of complex neuronal circuitry, and it is likely that a "cocktail" of treatments or cell types will be required (ie, cells of both glial and neuronal origin).²⁶ As a result, trials for spinal cord injury are likely to lie further into the future.

The way ahead

Although this report has focused on HNSCs, it is interesting to note that experimental animal studies are casting considerable light on many facets of adult neurogenesis. For example, it has been suggested that an interplay between astrocytes and the microenvironment may bring about adult neurogenesis.²⁷ Another study has concluded that hippocampal astrocytes provide a unique niche for adult neurogenesis.²⁸ These researchers further postulate that the capability for adult neurogenesis may lie in regionally specified astrocytes in the adult CNS providing appropriate signals. Such possibilities could also prove significant in humans.

HNSC biology is poised to make an impact on clinical neural transplantation programs. However, there is a grave danger that the rush to apply stem cell therapies in actual patients may lead to scientifically ill-founded clinical trials that lack adequate support from rigorous preclinical research.²⁵ Human trials should never be initiated prematurely in response to pressures from disabled patients, their doctors or families.

While the results with HNSCs (both embryonic and adult) have been very promising thus far, there are still hurdles to be overcome. We recommend that trials in human patients should not be initiated until:



The in-vitro manipulation of HNSCs becomes more sophisticated — it needs to be shown that desired neuronal phenotypes (eg, dopamine-producing neurones) can be reliably cultured, on demand, and in clinically significant quantities;



More convincing and clinically relevant animal studies are carried out — clinical trials should not be initiated on the basis of results from a limited number of rodent studies; and



Neurological testing shows *significant* and *long-lasting* functional recovery after transplantation experiments in well-characterised animal models of human CNS disorders.

It is only once such proof-of-concept has been demonstrated for stem cells in both culture systems and well-documented animal models of human CNS injury and disease that clinical trials with adult HNSCs will be scientifically and ethically justified.

Competing interests

None identified.

References

1. Eriksson P, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nature Med* 1998; 4: 1313-1317. <PubMed>
2. Fricker J. Human neural stem cells on trial for Parkinson's

- disease. *Mol Med Today* 1999; 5: 144. <PubMed>
3. Carpenter MK, Cui X, Hu ZY, et al. *In vitro* expansion of a multipotent population of human neural progenitor cells. *Exp Neurol* 1999; 158: 265-278. <PubMed>
 4. Fricker RA, Carpenter MK, Winkler C, et al. Site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain. *J Neurosci* 1999; 19: 5990-6005. <PubMed>
 5. Vescovi AL, Parati EA, Gritti A, et al. Isolation and cloning of multipotential stem cells from the embryonic human CNS and establishment of transplantable human neural stem cell lines by epigenetic stimulation. *Exp Neurol* 1999; 156: 71-83. <PubMed>
 6. Flax JD, Aurora S, Yang C, et al. Engraftable human neural stem cells respond to developmental cues, replace neurons, and express foreign genes. *Nature Biotech* 1998; 16: 1033-1039.
 7. Svendsen CN, Caldwell MA, Ostenfeld T. Human neural stem cells: isolation, expansion and transplantation. *Brain Pathol* 1999; 9: 499-513. <PubMed>
 8. Uchida N, Buck D, He D, et al. Direct isolation of human central nervous system stem cells. *Proc Natl Acad Sci USA* 2000; 97: 14720-14725. <PubMed>
 9. Johansson CB, Momma S, Clarke DL, et al. Identification of a neural stem cell in the adult mammalian central nervous system. *Cell* 1999; 96: 25-34. <PubMed>
 10. Kukekov V, Laywell E, Suslov O, et al. Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of the adult human brain. *Exp Neurol* 1999; 156: 333-344. <PubMed>
 11. Roy NS, Benraiss A, Wang S, et al. Promoter-targeted selection and isolation of neural progenitor cells from the adult human ventricular zone. *J Neurosci Res* 2000; 59: 321-331. <PubMed>
 12. Akiyama Y, Honmou O, Kato T, et al. Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. *Exp Neurol* 2001; 167: 27-39. <PubMed>

13. Arsenijevic Y, Villemure J-G, Brunet J-F, et al. Isolation of multipotent neural precursors residing in the cortex of the adult human brain. *Exp Neurol* 2001; 170: 48-62. <PubMed>
14. Quinn S, Walters W, Vescovi A, et al. Lineage restriction of neuroepithelial precursor cells from fetal human spinal cord. *J Neurosci Res* 1999; 57: 590-602. <PubMed>
15. Villa A, Snyder EY, Vescovi A, et al. Establishment and properties of a growth factor-dependent, perpetual neural stem cell line from the human CNS. *Exp Neurol* 2000; 161: 67-84. <PubMed>
16. Svendsen CN, Caldwell MA. Neural stem cells in the developing central nervous system: implications for cell therapy through transplantation. *Prog Brain Res* 2000; 127: 13-34. <PubMed>
17. Studer L, Tabar V, McKay R. Transplantation of expanded mesencephalic precursors leads to recovery in parkinsonian rats. *Nat Neurosci* 1998; 1: 290-295. <PubMed>
18. Daadi M, Weiss S. Generation of tyrosine hydroxylase-producing neurons from precursors of the embryonic and adult forebrain. *J Neurosci* 1999; 19: 4484-4497. <PubMed>
19. Wagner J, Akerud P, Castro DS, et al. Induction of a midbrain dopaminergic phenotype in Nurr1-overexpressing neural stem cells by type 1 astrocytes. *Nature Biotech* 1999; 17: 653-659.
20. Svendsen C, Caldwell M, Shen J, et al. Long term survival of human central nervous system progenitor cells transplanted into a rat model of Parkinson's disease. *Exp Neurol* 1997; 148: 135-146. <PubMed>
21. Brustle O, Choudhary K, Karram K, et al. Chimeric brains generated by intraventricular transplantation of fetal human brain cells into embryonic rats. *Nature Biotech* 1998; 16: 1040-1044.
22. Qu T, Brannen C, Kim H, et al. Human neural stem cells improve cognitive function of aged brain. *Neuroreport* 2001; 12: 1127-1132. <PubMed>
23. Svendsen C, Clarke D, Rosser A, et al. Survival and differentiation of rat and human epidermal growth-factor responsive precursor cells following grafting into the lesioned

- adult central nervous system. *Exp Neurol* 1996; 137: 376-388. <PubMed>
24. Palmer T, Takahashi J, Gage F. The adult rat hippocampus contains primordial neural stem cells. *Mol Cell Neurosci* 1997; 8: 389-404. <PubMed>
 25. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. *Nature Neurosci* 2000; 3: 537-544. <PubMed>
 26. Jones DG, Galvin KA. The brave new world of central nervous system regeneration. *N Z Med J* 2001; 114: 340-342. <PubMed>
 27. Alvarez-Buylla A, Garcia-Verdugo JM. Neurogenesis in adult subventricular zone. *J Neurosci* 2002; 22: 629-634. <PubMed>
 28. Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 2002; 417: 39-44. <PubMed>

(Received 31 Jan 2002, accepted 6 Jun 2002)

**Department of Anatomy and Structural Biology,
University of Otago, Dunedin, New Zealand.**

**Kerry A Galvin, BSc(Hons), PhD, Junior Research Fellow; D Gareth Jones,
MBBS, DSc, Professor, and Head of Department.**

Correspondence: Professor D G Jones, Department of Anatomy and Structural Biology, University of Otago, PO Box 913, Dunedin, New Zealand.
gareth.jones@stonebow.otago.ac.nz